and 32 have also been amended to clarify that the endothelial cells are those which have been "cytokine-activated", where this terminology is supported throughout the Specification such as, e.g., page 14, line 13 ("IL-1β activated HUVE cells"); page 45, lines 22-25 ("LYMPHOCYTE ADHESION TO ACTIVATED ENDOTHELIUM IS MEDIATED BY..." and, "activated with a variety of cytokines" at page 45, line 28), and elsewhere. No new matter is presented thereby and entry is respectfully requested.

The Specification has been objected to and claims rejected under 35 USC § 112, and the amendment of 9/20/95 objected to under 35 USC § 132, due to the previously proposed insertion of the negative limitation in claims 1 and 32 of "other than those lining high endothelial venules (HEV)." Applicant believes the Specification is clear that endothelial cells lining high endothelial venules (HEV), i.e., those of lymphocyte homing tissue, were not subjected to activation by inflammatory cytokines. Applicant also notes that under 35 USC § 132 the question is not whether the objected to phrase was <u>used</u> in the Specification as filed, but whether there is <u>support</u> in the Specification for employment of the phrase in a claim, i.e., is the concept present in the original disclosure? <u>In re Anderson</u>, 176 USPQ 331, 336 (CCPA 1973). In the present case Applicant believes the concept of the

proposed negative limitation of "other than those lining high endothelial venules (HEV)" is clearly supported in the Specification as filed. Moreover, as for the rejection of the claims based on the written description requirement of §112, first paragraph, one need only reasonably convey to one having ordinary skill in the art that an applicant had possession of the now claimed subject matter. Adequate description under the first paragraph of Section 112 does not require literal support for the claimed invention. Ex parte Parks, 30 USPQ 2d 1234 (Bd. Pat. Appl. Inter. 1993). Thus, while Applicant disagrees with the basis for the objection and rejection, it has been obviated by the amendment to claims 1 and 32.

Paragraphs 21-23 of the Office Action set forth rejections based on provisional double patenting or obviousness-type double patenting over the claims of Applicant's USSN 0847,777. This application is being abandoned in favor of the present application, and thus the rejections are obviated.

In paragraph 27 of the Office Action, claims 1-3 are rejected under 35 USC § 102(a) over Holzmann et al. (Immunol. Rev. 1989). The Office states that Holzmann teaches that the VLA-4α-specific antibody P4C2 inhibits lymphocyte binding to Peyer's patch high endothelial venules (HEVs), therefore the

inhibition of lymphocyte-endothelial adherence by an α4β1-specific antibody "is meant by the reference." As previously noted by Applicant (Amendment of December 7, 1993), Holzmann's HEVs were in a normal resting state, i.e., non-activated. In contrast, the present claims are drawn to inhibiting lymphocyte binding to cytokine-activated endothelial cells. Activation of endothelial cells induces surface expression of endothelial cell-leukocyte adhesion molecules, and thus activated endothelial cells have leukocyte binding capabilities not present in non-activated endothelial cells. Thus, the presently claimed invention cannot be anticipated by the teachings of Holzmann, and withdrawal of this rejection is respectfully requested.

Claims 1-5, 32 and 34-36 stand rejected as allegedly obvious over Holzmann (Immunol. Rev. 1989) and Holzmann (Cell, 1989) in view of Butcher, Hemler and Takada. The Holzmann references, new primary references, are relied on as teaching the blocking of lymphocyte adhesion to HEV with α4-specific antibodies as well as the role of both α4-specific β1-specific events in lymphocyte-endothelial interactions and blocking these events by antibodies. The secondary references of Butcher, Hemler and Takada have been discussed previously.

The present invention involves methods for inhibiting the adherence of lymphocytes to cytokine-activated endothelial cells. The HEVs of Holzmann were not cytokine-activated, as would occur in the context of an inflammatory response. As noted above, activated endothelial cells have leukocyte binding capabilities not present in non-activated endothelial cells. Thus, the ability to inhibit binding of leukocytes to non-activated endothelial cells does not suggest the ability to inhibit binding of leukocytes to activated endothelial cells. Moreover, the monoclonal antibody to LPAM-1 only inhibited binding of lymphoid cells to resting Peyer's patch HEVs, not resting peripheral node HEVs. All of the antibodies tested by Holzmann et al. (Fig. 2) were tested on resting Peyer's patch HEVs (and in the context of human lymphoma cells interacting with murine Peyer's patches cells, not human on human as suggested by the Office). Thus, there is no reason to believe based on the Holzmann papers that the adherence of lymphocytes to cytokine-activated endothelial cells could be inhibited by exposing the lymphocytes to an antibody or antigen-binding fragment that binds to $\alpha_4\beta_1$.

The comment by the Office (page 7) that Holzmann purportedly teaches that the structure of LPAM-1 is "virtually identical" to that of human VLA-4 does not appear to find support in the Holzmann Cell paper. In fact, the Holzmann

Immunol. Rev. paper shows that LPAM-1 has a new β subunit (p. 52). Further, the Introduction of the Holzmann Cell paper is said to teach that integrin specific antibodies including the β1-specificity inhibit lymphocyte endothelial interactions and lymphocyte adherence/migration. In fact, it appears that the integrin specific antibodies discussed in the Introduction are directed towards integrins that have an entirely different β-chain.

The secondary references add nothing further to the teachings of Holzmann which would suggest the instantly claimed methods. Applicant notes that the prior rejection under § 103, which was based on the same three references that are now used as secondary to the Holzmann articles, was withdrawn in the present Action.

Turning to the secondary references in the context of their combined teachings, it can be seen that Butcher teaches the binding of a MEL-14 antibody to a murine lymphocyte surface receptor, but this is a homing receptor known as $gp90^{mel-14}$, not the $\alpha_4\beta_1$ of the present invention. The Office relies on Butcher for the "similarity of this system" to VLA-4 and lymphocyte-endothelium interactions. While perhaps similar in some respects, there is absolutely no indication or suggestion in any combination of Butcher taken

with the Holzmann references, however, that an antibody to $\alpha_4\beta_1$ could be employed to inhibit adherence of lymphocytes to cytokine-activated endothelial cells.

Hemler (EP 330,506) actually teaches away from the present invention, in that it suggests, on page 5, para. 4, that the VLA proteins interfere with cell attachment mechanisms, and more particularly to matrix proteins, rather than employing antibodies to the VLA proteins. Thus, the disclosure does not appear to suggest an analogous system, and no motivation appears to combine its teachings with those of the other references, much less in a manner which suggests the claimed invention.

Takada (Nature 1987), as discussed previously by Applicant, refers to studies done to determine whether VLA proteins mediate cell adhesion to matrix proteins. Takada refers to the cross-reactivity of anti-fibronectin receptor antibodies with the common β unit of VLA proteins, but Takada makes no reference to immune responses or to lymphocyte binding to activated endothelial cells. And, as with Hemler, Takada suggests that VLA heterodimers may function in binding to matrix proteins, teaching away from the present invention. None of the references cited by the Office suggest that, taken with the Holzmann articles, the adherence of lymphocytes to

cytokine-activated endothelial cells could be inhibited by an antibody to $\alpha_4\beta_1$.

Thus, the presently claimed invention cannot be said to be suggested by the combined teachings of Holzmann and Holzmann in view of Butcher, Hemler and Takada, and withdrawal of this rejection is respectfully requested.

Applicant reserves the right to antedate the Holzmann references under 37 CFR § 1.131 should this basis of rejection be maintained in a subsequent action on the merits.

In view of the above amendments to the claims and accompanying remarks, Applicant believes that each rejection has been addressed and overcome and that the application is now in condition for allowance. Notice to that effect is requested. If for any reason, however, the Examiner feels that a telephone conference would expedite prosecution of the subject application, the Examiner is invited to telephone the undersigned at 206/467-9600.

Respectfully submitted,

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By: Steven W. Parmelee
Steven W. Parmelee
Reg. No. 31,990

TOWNSEND and TOWNSEND and CREW
Two Embarcadero Center, 8th Floor
San Francisco, CA 94111-3834